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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JAMES P. NAKAS,
STUART W. TANENBAUM,
and
THOMAS KEENAN,
Appellants[1]

Appeal 2010-000356
Application 10/528,923
Technology Center 1600

Before ERIC GRIMES, CAROL A. SPIEGEL, and
MELANIE L. McCOLLUM, *Administrative Patent Judges.*

SPIEGEL, *Administrative Patent Judge.*

DECISION ON APPEAL[2]

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[1] The real party in interest is the RESEARCH FOUNDATION OF THE STATE UNIVERSITY OF NEW YORK. (Brief of Appellant filed 15 April 2009 ("Br.") at 1). This decision also cites to the Examiner's Answer mailed 10 July 2009 ("Ans.").

[2] The two-month period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

Appellants appeal under 35 U.S.C. § 134(a) from an Examiner's final rejection of claims 1, 3-7, 9, and 18. Claims 10-17, the only other pending claims, stand withdrawn from consideration as directed to a non-elected invention. We have jurisdiction under 35 U.S.C. § 134. We AFFIRM.

I. Statement of the Case

The subject matter on appeal is directed to a method of producing polyhydroxyalkonates ("PHAs") by bacterial fermentation using xylose and levulinic acid ("LA") as primary and secondary carbon sources, respectively. Claims 1 and 9 are illustrative and read (Br. 8-9, emphasis added):

> 1. A process for producing a polyhydroxyalkonate (PHA) co-polymer comprising 3-OH-valeryl (3-HV) and 3-OH-butyryl (3-HB) monomers which comprises
>
> adding to a medium containing a microorganism that converts carbon to PHA a quantity of xylose as a primary carbon source and a first quantity of levulinic acid as a secondary carbon source;
>
> *adding a second quantity of levulinic acid to the medium between about 16 hours and about 24 hours after the first quantity of levulinic acid is added,*
>
> *wherein the second quantity of levulinic acid is greater than the first quantity of levulinic acid.*
>
> 9. The process of claim 1 in which the ratio of xylose to levulinic acid in the medium after the second quantity of levulinic acid is added ranges from about 0.01 to about 1.0.

The Examiner rejected claim 9 as confusing under 35 U.S.C. § 112, second paragraph, and claims 1, 3-7, 9, and 18 as obvious under 35 U.S.C. §

103(a) over the combined teachings of Lee,[3] Ramsay,[4] Bertrand,[5] Chung,[6] and Jang[7] (Ans. 3-8).[8]

As to the rejection of claim 9 under § 112, second paragraph, the Examiner stated in the Final Rejection that

> Claim 9 is confusing in the recitation of "the ratio of xylose to levulinic acid in the medium after the second addition of levulinic acid is from about 0.01 to 1.0" ... It would appear that this should recite the ratio of levulinic acid to xylose. This rejection has been previously presented as an objection since it appeared to be simply a typographical error but as applicant has twice not corrected the problem it is now made a rejection as

[3] Sang Yup Lee, *Poly(3-hydroxybutyrate) production from xylose by recombinant Escherichia coli*, 18 BIOPROCESS ENGINEERING 397-399 (1998) ("Lee").
[4] Ramsay et al., *Hemicellulose as a potential substrate for production of poly(β-hydroxyalkanoates)*, 41 (Suppl. 1) CANADIAN JOURNAL OF MICROBIOLOGY 262-266 (1995) ("Ramsay").
[5] Bertrand et al., *Biosynthesis of Poly-β-Hydroxyalkanoates from Pentoses by Pseudomonas pseudoflava*, 56 APPLIED AND ENVIRONMENTAL MICROBIOLOGY 3133-3138 (October 1990) ("Bertrand").
[6] Chung et al., *Effect of Levulinic Acid on the Production of Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) by Ralstonia eutropha KHB-8862*, 39 THE JOURNAL OF MICROBIOLOGY 79-82 (March 2001) ("Chung").
[7] J.-H. Jang and P.L. Rogers, *Effect of Levulinic Acid on Cell Growth and Poly-β-hydroxyalkanoate Production by Alcaligenes SP. SH-69*, 18 BIOTECHNOLOGY LETTERS 219-224 (February 1996) ("Jang").
[8] The Examiner entered a claim amendment filed with Appellants' Brief which overcame the rejection of claims 1, 3-7, 9, and 18 under 35 U.S.C. § 112, second paragraph, set forth on pages 3-4 of the Office action mailed 16 January 2009 (Final Rejection or "FR"), but not the rejection of claim 9 set forth on pages 4-5 (Ans. 3-4). To the extent Appellants may not have appreciated that the latter rejection of claim 9 was maintained, Appellants had the opportunity to file a Reply Brief in response to the Examiner's Answer. No Reply Brief was filed.

> applicants [sic] lack of correction imply this is not the case. [FR 4-5.].

Since Appellants have not requested review of this rejection (Br. 3), we summarily sustain the rejection of claim 9 as unpatentable under 35 U.S.C. § 112, second paragraph.

As to the obviousness rejection, Appellants argue that the applied prior art fails to teach or suggest adding a second quantity of LA in an amount greater than the first quantity subsequent to the first quantity as claimed (Br. 6). Appellants further argue Chung explicitly teaches away from the claimed subject matter by maintaining the level of LA at a constant amount (*id.*). Thus, Appellants contend that there is no reason to combine or modify the teachings of the applied prior art based on either the prior art or ordinary knowledge in the art (*id.* at 7).

Therefore, the dispositive issue is whether the evidence of record supports a conclusion that it would have been obvious to one of ordinary skill in the art to add a second, larger quantity of LA subsequent to the first quantity in a fermentation process for producing a PHA copolymer as claimed.

II. Findings of Fact

The following findings of fact ("FF") are supported by a preponderance of the evidence of record.

[1] Chung teaches that

> Poly-ß-hydroxyalkanoates (PHAs), a family of polyesters produced by a variety of microorganisms, have … potential application as biodegradable and biocompatible thermoplastics. In particular, a copolyester consisting of 3-hydroxybutyrate (3HB) and 3-hydroxyvalerate

> (3HV) … has been of the greatest commercial interest since this polyester exhibits a considerable range of thermomechanical properties, which depend on its 3HV content. Production of poly(3HB-*co*-3HV) is usually achieved by providing bacteria with a cosubstrate, such as propionate and valerate, along with a main carbon source. … [Chung 79, ¶ 1, endnotes omitted.]

[2] According to Bertrand, "the accumulation of the polymer is triggered by limitation of a nutrient such as oxygen or nitrogen", e.g., after about 15 to 20 hours of culture (Bertrand 3133, ¶ 2, endnotes omitted; Fig. 2).

[3] Further according to Bertrand, poly(3HB-*co*-3HV) can be produced by adding propionic acid and glucose to nitrogen-limited cultures of *Alcaligenes eutrophus* (*id.* at ¶ 3) and that PHA production cost largely depends on the carbon source used (*id.* at ¶ 4).

[4] Thus, replacing the traditional carbon sources with an inexpensive substrate could significantly reduce production cost (*id.*).

[5] Bertrand teaches that when *Pseudomonas pseudoflava* was grown on xylose, an inexpensive hemicellulosic sugar, as the sole carbon source, the specific growth and poly(3-hydroxybutyrate) ("PHB") production rate was four times slower than with glucose but the final PHB content was similar to that measured for the glucose fermentation (*id.* at 3133, ¶ 4; 3135, ¶ 3; Fig. 2; 3137, ¶¶ 3-4).

[6] Similarly, Ramsay teaches that *Pseudomonas cepacia* can use xylose to produce PHAs (Ramsay abstract).

[7] According to Ramsay, "[w]hen grown on xylose, *P. cepacia* exhibited similar behaviour to that on hexoses [e.g., glucose or fructose] with no

detectable PHB accumulated until the NH_4^+ concentration had fallen to less than 0.18 $g{\cdot}L^{-1}$ (Fig. 1)," in approximately 20 hours (*id.* at 264, last full sentence; Fig. 1).

[8] Ramsay concluded that use of xylose as the main carbon source would reduce the substrate cost by more than half compared to glucose to a level comparable to that of molasses (*id.* at 265, last ¶).

[9] Lee teaches using a recombinant *Escherchia coli* bacteria transformed with the *A. eutrophus* PHA biosynthesis genes to produce PHA, specifically PHB, from xylose (Lee abstract).

[10] Jang discloses a two stage continuous culture with controlled substrates feeding wherein *Alcaligenes* sp. SH-69 was cultured in the first stage with glucose, followed by supplementing the glucose with LA in the second stage (Jang 220, ¶ 5).

[11] "Depletion of nitrogen source in the medium in the second stage fermentation in the presence of excess carbon was allowed to occur … [in view of previous reports] that these conditions would enhance accumulation of PHA" (*id.* at 223, ¶ 1).

[12] Jang concludes not only that LA can be used as a precursor of 3HV, but also that LA has a larger stimulatory effect on PHA synthesis than propionic acid (*id.* at 222, ¶ 2; 224 ¶ 2).

[13] Jang also concludes that the composition and concentration of the copolymer can be manipulated by varying the LA/glucose ratio in the feed to the second stage, thereby producing biopolymers with a range of characteristics (*id.* at 224, ¶ 2).

[14] Similarly, Chung teaches that "… LA is a better cosubstrate for cell growth as well as for poly(3HB-*co*-3HV) production than the

conventionally used cosubstrates such as propionate and valerate" (Chung 81, ¶ 1).

[15] Both Jang and Chung teach that relatively low concentrations of cosubstrates inhibit bacterial growth (Jang 219, ¶ 1; Chung 80, ¶ 5).

[16] Chung also teaches that adding LA repeatedly into a fermentor culture to maintain its concentration resulted in significantly higher copolyester content and 3HV yield than when the same concentration of LA was supplied all at once (*id.* abstract; 81, ¶ 3).

[17] "However, in the case of repeated addition of LA, the final 3HV mol% in the copolyester decreased to 28 mol%, which was due to the remarkable increase of cell and PHA content during the cultivation" (*id.*).

III. Discussion

A. Legal principles

"The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In determining whether obviousness is established by combining the teachings of the prior art, "the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller,* 642 F.2d 413, 425 (CCPA 1981). Furthermore, the "[obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550

U.S. 398, 418 (2007). A person of ordinary skill must be presumed to have some skill, *In re Sovish*, 769 F.2d 738, 743 (Fed. Cir. 1985), and ordinary creativity, *KSR*, 550 U.S. at 418.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

B. Analysis

Bertrand, Ramsay, and Lee all teach using xylose as a primary carbon source (substrate) for bacterial production of PHAs (FF 5, 6, 9). Bertrand and Ramsay also teach that accumulation of PHAs is triggered by decreased nitrogen content in the culture media at about 15 to 20 hours (FF 2, 7). Bertrand and Ramsay expressly teach that xylose is a cost effective alternative to conventional substrates, e.g., glucose (FF 3-5, 8). Jang and Chung both teach that LA is a better cosubstrate than conventionally used substrates, e.g., propionate and valerate, for production of a PHA copolymer of great commercial interest because of its range of thermochemical properties, poly(3HB-*co*-3HV) (FF 1, 12, 14). Chung also teaches that adding LA to the bacterial fermentation culture over time results in a significantly higher copolyester content and 3HV yield (FF 16). Both Chung and Jang teach that the ratio of 3HV to 3HB in the copolymer can be modulated by adjusting the ratio of primary and secondary carbon sources (FF 13, 17). Both Chung and Jang teach that relatively low levels of cosubstrates inhibit bacterial growth (FF 15). However, Chung suggests that when LA is repeatedly added over time to maintain a constant LA level

(rather than adding the same amount of LA all at once), the final 3HV and copolyester concentrations decrease due to increased cell and PHA content during the cultivation (FF 17).

Thus, it would have been obvious to one of ordinary skill in the art to produce poly(3HB-*co*-3HV) by bacterial fermentation using xylose as the primary carbon source (Bertrand, Ramsay, Lee) because it is cheaper than other conventionally used substrates of 3HB (Bertrand, Ramsay) and LA as a secondary carbon source of 3HV (Jang and Chung). It would have been further obvious to add a small amount of LA initially followed by a larger amount about 16 to 24 hours later to minimize inhibition of bacterial growth in the first stage of fermentation (Jang and Chung) and to stimulate PHA production in the second stage of production and/or provide a desired level of 3HV for producing a copolymer with desired thermochemical properties (Jang and Chung). Appellants' arguments do not persuade us otherwise.

The Examiner has provided sound reasoning for combining the teachings of the references, i.e., xylose is a cheap primary carbon source, LA is a more effective cosubstrate than propionate or valerate, and adjusting the amount of LA added in the first and second fermentation stages to maximize PHA production (Ans. 8-10). We also note that Chung teaches that, in the case of repeated addition of LA, the final 3HV mol% in the copolyester decreased to 28 mol% (FF 17); and, both Jang and Chung teach that the relative ratio of cosubstrate/primary carbon source is a result effective variable vis-à-vis the composition of the resulting copolymer (FF 13, 17). Finally, Appellants' argument that Chung teaches away by maintaining a constant level of LA during fermentation is not persuasive. Chung suggests that it is undesirable to add the total amount of LA as a single, initial

addition. Chung does not say that it is undesirable to add increasing amounts of LA over time or that this approach will not work, and so does not teach away. *Gurley*, 27 F.3d at 553. Silence cannot be interpreted as a teaching away.

C. Conclusion

We will sustain the rejection of claims 1, 3-7, 9, and 18 as obvious under § 103(a) over Bertrand, Ramsay, Lee, Jang, and Chung. The evidence of record supports a conclusion that it would have been obvious to a skilled artisan to add a second, larger quantity of LA subsequent to the first quantity in a fermentation process for producing a PHA copolymer as claimed.

IV. Order

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner to reject claim 9 as unpatentable under 35 U.S.C. § 112, second paragraph, is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 1, 3-7, 9, and 18 as obvious under 35 U.S.C. § 103(a) over the combined teachings of Lee, Ramsay, Bertrand, Chung, and Jang is AFFIRMED; and,

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(vi).

AFFIRMED

cdc

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